EDITORIAL

Condomless Sex With Virologically Suppressed HIV-Infected Individuals
How Safe Is It?

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The use of antiretroviral therapy (ART) across the globe has had a profound influence on the natural history of HIV infection. Although the pandemic continues to spread, one of the greatest advances in prevention since the use of ART in pregnancy to avoid vertical transmission was the recognition that the same treatment prevents horizontal transmission. Many cohorts have suggested this benefit,[1,2] findings that in part led to the Swiss Commission statement in 2008 that HIV-infected individuals who have had suppressed plasma HIV RNA load for longer than 6 months and who do not have sexually transmitted infections (STIs) were not sexually infectious.[3] Although the statement was controversial at the time, the cohort data were compelling, and there have been very few case reports of an HIV transmission event from a virologically suppressed person and no events identified in a systemic review of patients with suppressed plasma HIV RNA load in cohort studies and randomized controlled trials.[4]

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The results of a large randomized clinical trial of early vs deferred ART in the HIV-infected partner in serodiscordant couples, the HIV Prevention Trials Network (HPTN) 052, further demonstrated the low risk of transmission from HIV-infected patients receiving ART. This study was stopped prematurely when the investigators found that early therapy was associated with a 96% reduction in risk of transmission to the uninfected partner.[5] Final study results showed a 93% reduced risk of HIV transmission and no transmission events from those who were virologically suppressed while taking ART.[6] Although these findings supported the potential public health benefits of ART, the study did not fully address the question as to whether patients with plasma HIV RNA suppression can have condomless sex without concern for transmitting HIV. The study primarily included heterosexual couples, making it impossible to extrapolate results to other groups, such as men who have sex with men (MSM). In addition, the study design included a comprehensive prevention package that included regular counseling about safe sex, testing for and treatment of STIs, and frequent testing for HIV, along with provision of condoms to all study participants and encouragement for their use.

In this issue of *JAMA*, Rodger and colleagues[7] report data from the PARTNER study, a prospective, observational cohort of 1166 serodiscordant couples with the HIV-infected partner receiving ART and having plasma HIV RNA levels less than 200 copies/mL. These couples were recruited from 75 European sites between September 2010 and May 2014 and included only those who reported routine engagement in condomless sex. The analyses included 888 couples with 1238 couple-years of follow-up (median, 1.3 years); 340 MSM and 548 heterosexual couples (269 HIV-infected male partners and 279 HIV-infected female partners). At study entry, the couples reported condomless sex for a median of 2 years (interquartile range, 0.5-6.3 years); during the course of follow-up, the couples reported approximately 40 000 condomless sex acts. The main finding was that 11 uninfected partners became infected with HIV, 10 among MSM and 1 among the heterosexual partners. Notably, none of these infections proved to involve viruses phylogenetically linked to the HIV-infected study partner. As a result, the authors concluded that there were no transmission events from virologically suppressed HIV-infected participants to their uninfected partners.

The PARTNER study by Rodger et al[7] addresses some of the important limitations of HPTN 052. For example, this cohort included MSM and demonstrated no within-couple HIV transmission events within the group. In addition, unlike HPTN 052, in which ART was used as an adjunct to a strong safe sex message, the PARTNER study enrolled individuals who admitted to primarily engaging in condomless sex with their partners. However, the biology of HIV transmission and human behavior is complicated, and it is inevitable that enrollment into a study, even a cohort study, has a potential influence on these factors.

The PARTNER study also has several limitations that must be considered in its interpretation and potential clinical application. First, despite the impressive effort to enroll a large and diverse group of individuals, the study had limited power. The authors note that despite a rate of 0 for within-couple HIV transmission, the upper 95% confidence limit for within-couple transmissions per 100 eligible couple-years of follow-up for heterosexuals was 0.97 for the male HIV-positive/female HIV-negative couple group, 0.88 for the female HIV-positive/male HIV-negative couple group, and 0.84 for the MSM couple group. For persons engaging in receptive anal sex with ejaculation inside the uninfected partner, the upper 95% confidence limit for within-couple HIV transmission was 2.7 per 100 couple-years of follow-up; however, this estimate was based on relatively small numbers, because only 45% of the MSM group reported this type

of sexual behavior. Even though there were no transmission events, the upper confidence limit reflects the small sample size, so that the estimated risk of transmission via this route is relatively imprecise.

A second limitation of the PARTNER study is that the study population represented a select group that may be different than HIV-serodiscordant couples encountered in other settings. For example, it is possible that couples with stable relationships may be at lower risk for HIV transmission. This is supported by the differences in transmission rates observed in the control groups of studies of preexposure prophylaxis. For instance, among serodiscordant couples enrolled in the Partners PrEP study, the incidence of HIV transmission was 1.99 per 100 patient-years of follow-up[8] compared with other high-risk heterosexual individuals enrolled in the TDF2 and VOICE studies, in which the incidence of HIV transmission was approximately 3 to 6 per 100 patient-years of follow-up.[9,10] The couples enrolled in the PARTNER study reported condomless sex for a median time of 2 years at baseline; thus, those at particularly high risk might have transmitted HIV earlier and been systematically excluded from the study. Additionally, HIV-infected partners had been receiving ART for a considerable length of time at baseline, a median of 7.5 years (interquartile range, 3.3-14.2 years), a factor that may influence the likelihood of transmission. Mujugira and colleagues[11] showed that among the HIV-infected partners in the control group who initiated ART in Partners PrEP the risk of transmission remained high among those who received therapy for less than 6 months; the incidence of HIV transmission per 100 person-years of follow-up was 2.08 prior to starting ART, 1.79 during the first 6 months of therapy, and then was 0 among those treated for longer than 6 months, although the patient-years of follow-up were relatively short in the latter 2 groups. It is conceivable that the longer an HIV-infected person is receiving ART, the less likely that person might be to transmit HIV to their partners.

Another characteristic of the PARTNER study cohort is the high level of self-reported adherence to ART, ranging from 93% to 97% for the various risk groups. This level of treatment adherence may exceed that seen in the community at large. For example, Marks et al[12] evaluated more than 14 000 patients receiving therapy in multiple clinics between 2009 and 2013 and found that nearly 25% of the time the patients had plasma HIV RNA levels greater than 1500 copies/mL, which based on other cohorts would put them at increased risk for transmission.[13]

Although the PARTNER study enrolled individuals who self-reported having condomless sex with their partner, the uninfected partner did receive counseling at every visit regarding the risk of condomless sex and was strongly encouraged to consistently use condoms. In addition, patients were drawn from a population of individuals who were receiving care and presumably had testing and treatment for sexually transmitted infections STIs, which was not an uncommon event and could further reduce the risk of HIV transmission. In fact, the authors report that 115 of 680 (16.9%) among the MSM couples (including 59 with HIV and 56 without HIV) and 65 of 1096 (5.9%) among the heterosexual couples (including 32 with HIV and 33 without HIV) acquired STIs during the course of follow-up. It is difficult to know with certainty how these factors could have influenced the outcome of this study.

After considering the results of the PARTNER study and the strengths and weaknesses of the existing data, clinicians and public health professionals need to formulate a message to share with HIV-infected individuals and their sexual partners. Certainly health care professionals should encourage all HIV-infected individuals to initiate and adhere to ART. Patients also could be informed that available data indicate that viral suppression along with the use of condoms results in an extraordinarily low risk of transmission among heterosexual couples and that although data are limited, this is likely to be true for MSM.

Clinicians can further emphasize to patients that the use of condoms is an important measure to prevent transmission of STIs and advise them that having a virologically suppressed partner does not protect the HIV-uninfected person from acquiring HIV from other individuals outside the relationship. The importance of the latter message is emphasized by the 11 nonphylogenetically linked transmission events observed in the PARTNER study by Rodger et al and the 20% of transmission events among nonstudy related partners observed in HPTN 052 by Cohen et al.[5]

For individuals who want to routinely or intermittently not use condoms with an HIV-infected partner, clinicians can indicate that the risk of HIV transmission appears small in the setting of continued viral suppression, emphasizing that the duration the HIV-infected partner needs to be virologically suppressed before achieving optimal protection is unknown, although appears to be for at least 6 months, based on the best available data. Moreover, clinicians need to be clear that even though the overall risk for HIV transmission may be small, the risk is not zero and the actual number is not known, especially for higher-risk groups such as MSM. Although more research is needed with larger numbers of couples and longer follow-up, it is not known if or when such data will emerge. Consequently, for now, clinicians and public health officials must share the data that exist in an honest and understandable way so that serodiscordant couples can be fully informed when individualizing their decision making about sexual practices.

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Antiretrovirals for HIV Treatment and Prevention
The Challenges of Success

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After the first case reports of AIDS were described in 1981, it soon became clear that the epidemic constituted a public health emergency. Although the first antiretrovirals were evaluated in clinical trials in the 1980s, it was not until the mid-1990s that the clinical efficacy of combination antiretroviral chemotherapy was demonstrated to prevent immunocompromise and to restore health to people living with AIDS. When the International Antiviral Society–USA (IAS-USA) published its first antiretroviral guidelines in *JAMA* in conjunction with the International AIDS Conference in Vancouver in 1996,[1] it represented the beginning of a new era, suggesting that the pandemic might be controlled by treatment. In the current issue of *JAMA*, the IAS-USA presents its most recent set of guidelines,[2] reflecting substantial changes over the past 20 years in the development of more potent combinations of drugs with fewer adverse effects, the advent of coformulated medications, and the evidence that antiretroviral agents have a vital role in HIV prevention.

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The new IAS-USA guidelines are particularly noteworthy in several regards. Based on data from the START[3] and TEMPRANO[4] trials and many observational studies, the expert panel recommends (as it did in its 2014 guidelines[5]) that all individuals who are diagnosed as having HIV infection should initiate treatment independent of CD4 cell count as soon as they are ready, and the sooner the better. This reflects an evolution in thinking. In earlier years, when the benefits of antiretroviral therapy were more limited and treatment-related toxic effects were more common, recommendations suggested that the drugs should not be used until individuals were at increased risk of immunosuppression. More recent studies suggest that the burden of chronic immune stimulation and inflammation that accompanies early asymptomatic HIV infection can result in long-term morbidity[6]; thus, earlier treatment is of great benefit to individuals. Moreover, other studies such as HPTN 052[7] have demonstrated that early initiation of antiretroviral therapy results in virologic suppression that makes HIV-infected people significantly less infectious to their partners. Thus, the prompt initiation of treatment has become a hallmark of a public health strategy to contain the epidemic ("treatment as prevention").

Another important point of the current guidelines is the recognition that a relatively newer class of antiretroviral agents, the integrase strand transfer inhibitor agents (InSTIs), are a cornerstone of the regimens for early initiation of antiretroviral therapy. The reason InSTIs have moved into a key position as first-line therapy is because these drugs have been shown to be highly effective, with the highest and most rapid rates of virologic suppression compared with protease inhibitors[8] and nonnucleoside reverse transcriptase inhibitors,[9] which previously had been mainstays of the antiretroviral "cocktail." Moreover, InSTIs are extremely well tolerated and several are coformulated with nucleoside analogs, allowing for potent, well-tolerated treatment to be delivered as a single pill taken once a day.

The new IAS-USA guidelines also discuss pharmacoeconomics. Currently, most antiretroviral combination regimens